acids, respectively (Wirak et al. (1991)). The Aβ protein segment comprises approximately half of the transmembrane domain and approximately the first 28 amino acids of the extracellular domain of an APP isoform.--

Please replace the two paragraphs beginning at line 23 of page 4 and ending at line 13 of page 5 with the following two rewritten paragraphs:

--Preferably, the protofibril or compound(s) with protofibril forming ability comprises the following amino acid sequence KLVFFAEDV (SEQ ID NO:2). The Aβ 1-42 fibrillisation process involves transitional conformation changes from α-helix via random coil to β-sheet. The stable α-helix sequence of residues 16-24 (KLVFFAEDV (SEQ ID NO:2)) apparently plays an important role in this process.

The protofibril or compound(s) with protofibril forming ability may be mutated or modified in relation to corresponding wild-type counterparts. Changes in the KLVFFAEDV (SEQ ID NO:2) sequence will affect the fibrillisation process. For example, changes of the charged amino acids Glu22 and Asp23 into neutral amino acids will induce a random coil structure in the Aβ peptide. Furthermore, deprotonation of other amino acids such as Asp7, Glu11 and His 6, 13 and 14 in the N-terminal end, has been

suggested to destabilize the α-helix, leading to initiation of the fibrillation process. Another example is mutations leading to increased immunogenicity in man by using amino acids from mouse Aβ at specific positions, e.g. Gly 5, Phe10, Arg13. Furthermore, amino acid 13 in Aβ is known to be part of a heparan sulphate binding motif (13-16; His, His, Gln, Lys) in human, which has been speculated to be involved in AD disease mechanism (inflammation) (Giulian et al. (1998)). In mouse, His 16 is exchanged for Arg 13 destroying the heparan sulphate binding site. Interestingly, mice have never been observed to develop AD. Hence, the use of Aβ-Arc/Arg13 as an immunogen would be a way to lower possible inflammatory side effects, elicited with Aβ peptides with intact heparan sulphate binding motif.--

Please replace the paragraph beginning at line 24 of page 10 with the following two rewritten paragraph:

--An APP mutation (E693G) in a family from northern Sweden, named the "Arctic" family, is identified, which spans over four generations. The family was screened for mutations in exons 16 and 17 of the APP gene by single strand conformation polymorphism analysis (SSCP) (L. Forsell, L. Lannfelt, (1995)). An abnormal mobility pattern was observed in exon 17. Sequencing revealed an A→G nucleotide

substitution, representing a glutamic acid to a glycine substitution at APP codon 693 (E693G), corresponding to position 22 in the A□ sequence. Venous blood was drawn into tubes containing EDTA and DNA was prepared according to standard procedures. SSCP was performed. To sequence exon 17 of the APP gene a 319 bp fragment was amplified with the following primers 5'-CCT CAT CCA AAT GTC CCC GTC ATT-3' (SEQ ID NO:3) and 5'-GCC TAA TTC TCT CAT AGT CTT AAT TCC CAC-3' (SEQ ID NO:4). The PCR products were purified with QIAquick PCR purification kit (Qiagen) prior to sequencing. Direct sequencing was performed in both 3′ and 5′ direction using the same primers and the BIG Dye cycle sequencing protocol (PE Biosystems) and were then analyzed on an ABI377 automated sequencer (PE Biosystems). The Arctic mutation was seen in one family and not in 56 controls or 254 cases with dementia. Carriers of the arctic mutation showed no vascular symptoms. The mutation was further verified by restriction analysis, since it destroyed a MboII restriction site. The mutation was fully penetrant as no escapees were found. Two-point linkage analysis was performed between the mutation and affection status in the family with an age-dependent penetrance, giving a lod score of 3.66 at recombination fraction 0.00. Two-point lod score was calculated using Mlink from the linkage package (version 5.1) at each of the following recombination fractions

0.00, 0.10, 0.20, 0.30 and 0.40 (q males=q females). A single-locus model with an autosomal dominant inheritance was assumed, which was compatible with the inheritance as it appeared in the pedigree. A cumulative age dependent penetrance was assigned from the known ages of onset in the family. Individuals were put into different liability classes depending on the age at onset (affected) or age at last examination (unaffected). The disease gene frequency and the marker allele frequency were estimated to be 0.001 and the phenocopy rate was set to 0.0001.--

(3 Cont'd

IN THE SEQUENCE LISTING

Please substitute the attached Sequence Listing, numbered as pages 1-2 for the Sequence Listing previously submitted.